REMARKS

Claims 42, 45-53, and 57-60 were previously pending in this application. By this amendment, Applicant is canceling claims 48 and 53 without prejudice or disclaimer. New claims 62-63 have been added. As a result, claims 42, 45-47, 49-52, and 57-63 are pending for examination with claims 42 and 59 being independent claims. No new matter has been added.

Support for wherein the subject is a human is found at least on page 19 lines 27-28.

The specification has been amended to correct the address of the ATCC as requested by the Examiner and to update the Related Application information.

Objection to Information Disclosure Statement (IDS)

The Examiner has indicated that some of the references cited on the October 4, 2004 IDS have not been considered. The Examiner requests that Applicants submit copies of the references cited in that IDS which were not initialed by the Examiner. Applicants enclose herewith a supplemental IDS with 1449 citing the references requested by the Examiner. It is applicants understanding that a fee is not requested for submission of the IDS because Applicants previously paid a fee with the submission of the October 4, 2004 IDS and met all the requirements of 37 CFR 1.98 at that time. If a fee is required, it may be charged to Applicants deposit account listed on the attached transmittal.

Rejections under 35 U.S.C. §112

Claims 42, 43-53 and 57-60 have been rejected under 35 U.S.C. §112 for a lack of enablement. According to the office action, the specification enables a method of redirecting an immune response from a Th2 to a Th1 response in a mouse using SEQ ID No.10, but that a method in humans and other animals and using other CpG oligonucleotides is not enabled.

In several places in the rejection it is suggested that a method for redirecting a Th2 to a Th1 immune response is equivalent to treating asthma. For example, page 7 lines 3-5 of the office action states: "The specification does not teach that any of the other myriad of possibilities of CpG having the claimed formulas can be used to treat an asthmatic subject

(redirecting a Th2 to Th1 immune response), animal or human." Applicants wish to establish on the record that a method of redirecting a Th2 to a Th1 response is not equivalent to treating asthma. Establishment of a Th1 biased immune response while decreasing a Th2 immune response is useful in the treatment of asthma, however, it is also useful in other therapeutic contexts. For instance, a Th1 biased immune response is useful in an adjuvant setting. Traditional adjuvants such as alum produce a Th2 biased immune response. One of the benefits of the use of CpG oligonucleotides as an adjuvant is that a Th1 biased immune response is produced.

According to the office action, the claimed invention lacks enablement because 1) the specification does not teach that ODN other than SEQ ID NO 10 are useful in the methods and that CpG oligonucleotides can be administered alone, without an antigen, 2) the state of the art is unpredictable, and 3) one of skill in the art would not accept on its face that the working examples are correlative or representative of methods of treatment. Applicants address each of these issues.

Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject result in an aspect of the immune response being altered, with a Th1 response being favored. Greater than 40 CpG oligonucleotides having different sequences were tested and demonstrated to have immune stimulating activity. These data are described throughout the patent application. For instance, Table 5 shows induction of Th1 cytokines using several different oligonucleotides.

Applicants have included an extensive discussion in the specification regarding the class of CpG oligonucleotides and their ability to promote a Th1 biased immune response. Working examples demonstrating the use of oligonucleotides with different sequences are provided in the application. No evidence has been presented in support of the rejection that the use of other CpG oligonucleotides would be unpredictable. The rejection in the absence of such evidence is not sufficient to support a lack of enablement. The claimed methods encompassing CpG oligonucleotides is enabled by the specification as filed, at least as of the October 30, 1996 filing date of the parent US Patent 6,207,646.

On page 7 of the office action it is stated that it is not clear from Example 12 if "the CpG administered alone to an asthmatic will redirect the cytokine responses and therefore Th1 type immune responses." Applicants disagree.

In addition to asserting in the specification that CpG oligonucleotides when administered produce a Th1 biased immune response, Applicants have provided *in vitro* and *in vivo* data demonstrating the same. Most of the data results from experiments performed with CpG oligonucleotides alone, and not in conjunction with an antigen. Only Example 12 describes data obtained from the administration of a CpG oligonucleotide at the same time as an antigen. Priority application (now issued US Patent 6,207,646) includes 14 Figures and 10 Tables demonstrating *in vivo* or *in vitro* activity of CpG oligonucleotides. Of all of these data, only 1 set of experiments (exemplified in Figures 9-15, Example 12) was performed by administering a CpG oligonucleotide at the same time as an antigen was administered. The majority of this data is conducted using CpG oligonucleotides either *in vitro* or *in vivo* without the concurrent use or administration of an antigen.

An important aspect of Example 12 (the one example using a co-administration of CpG and antigen) of the instant patent application is that the CpG is acting as the therapeutic in the study. It is the CpG not the schistosome eggs that is producing this Th1 favored immune response. When schistosome eggs are administered to an animal in the absence of CpG oligonucleotides, a Th2 biased response and eosinophil influx occur. When the CpG oligonucleotide is administered to an animal primed for an asthmatic response, as is demonstrated in Example 12, a Th1 biased response is induced.

The methods for shifting to a Th1 immune response are described throughout the application in terms of the administration of CpG as a therapeutic. It is taught that an immune profile which is consistent with the promotion of a Th1 favored response is achieved through the administration of CpG oligonucleotides. Much of the experimental work examining shifts in cytokine induction were achieved using CpG alone without an allergen. For instance, CpG oligonucleotides were used alone without antigen/allergen to produce Th1 biased cytokine

induction in Table 5 and Table 13. No antigen was administered. Th1 cytokines include IFN-γ, TNF-α, IL12, and GM-CSF.

The Examiner has cited several papers in support of the lack of enablement rejection and in particular in support of the argument that the state of the art is unpredictable. McCluskie et al 1999 and Krieg et al 2000 have been cited in support of the rejection for the proposition that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. McCluskie et al is an article describing DNA vaccines against Hepatitis B virus. On page 296, the page identified by the examiner, the reference discusses the factors involved in influencing the Th bias of the response to DNA vaccines. One of the factors is the presence of CpG motifs. The pending claims do not encompass plasmid vectors (or DNA vaccines). The independent claims include limitations that exclude plasmid vectors (upper size limit of 100 and phosphate backbone modification). The issues of predictability and therapeutic effectivity are very different for CpG oligonucleotides and DNA vaccines.

Krieg et al was also cited in support of the argument that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. The office action specifically pointed to page 524 of the reference. Applicants do not see this teaching in the reference and respectfully request more information if the Examiner maintains the rejection in view of this reference. In fact the reference teaches on page 524 that "Unlike many vaccine adjuvants that have been extremely effective in mice but disappointing in humans, CpG DNA is also highly effective in higher primates." This teaching seems to support that the response to the administration of CpG oligonucleotides is consistent in different organisms. Furthermore, Krieg et al describe the usefulness of CpG oligonucleotides in producing a Th1 biased immune response. Page 524 of Krieg et al includes the following teaching:

> "These and subsequent studies have shown CpG DNA to be a more effective Th1-like adjuvant than complete Freund's, and to be effective with multiple types of antigens and routes of immunization including mucosal immunization (reviewed in Ref. 50). In fact, in a comparison of 19 different adjuvants, CpG DNA was

> found to be the strongest for inducing Th1-like immune response to tumor antigens[51]"
> and
> "The potent Th1 adjuvant effect of CpG can even override preexisting Th2 immune responses [5, 47]; it has been used as an adjuvant for allergy vaccines, where it induces Th1 responses to antigens in the presence of a preexisting Th2 response, leading to decreased symptoms following subsequent allergen inhalation ..... It should be stressed that CpG DNA is effective in asthma immunotherapy even when given as a stand-alone agent without allergen."

Two references were cited in order to demonstrate that CpG was associated with dangerous side effects. The Satoh et al. reference is an abstract describing a study in which CpG oligonucleotides are administered subcutaneously to mice in combination with DNFB treatment and looking at T cell mediated hypersensitivity responses. The other reference cited for this proposition, Wohleben, provides a favorable view of CpG oligonucleotides and its usefulness in the treatment of asthma. It is touted as the most promising of approaches in the abstract. Even the cited paragraph on page 620 relates to the expectation that CpG oligonucleotides will be effective in humans.

Several Phase I and II studies have been performed in humans to date. In particular subcutaneous administration, like that in the Satoh reference, has been performed in humans for a cancer trial. The data are described in Kim et al., Blood, volume 4, issue 11, abstract # 743, Nov. 16, 2004. Toxic effects that would halt further human trials were not observed, even though the patients were provided CpG oligonucleotides in very aggressive doses. The abstract concludes that "weekly doses up to 0.36 mg/kg have been well tolerated."

Weiner et al. is cited for the proposition that the molecular mechanism of CpG is unknown. It is generally believed in the field that CpG oligonucleotides are acting through TLR9. Regardless, knowledge of the mechanism isn't necessary.

Agrawal et al has been cited in support of the assertion that the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable. In particular, the examiner has identified pages 78-80 as being particularly relevant. Agrawal et al is a review article describing antisense oligonucleotides. The authors suggest on page 78 that

in order to reduce non-antisense related activity it is best to avoid CpG motifs. The authors also indicate that if it is not possible to avoid CpG motifs, then it is possible to make one of 3 modifications to reduce the CpG activity of the oligonucleotide. One of the suggested modifications is to replace the cytosine base of the CpG with a 5-methyl cytosine base. The instant specification teaches that a CpG containing oligonucleotide has an unmethylated C in the CpG motif. The claims require that the C of the CpG motif is unmethylated. The reference does not support the lack of enablement of the claimed invention.

Another recent paper, not raised in the instant rejection by the Examiner is Jain & Kline. Jain & Kline provides a good description of the effects of CpG in the asthmatic airway. For instance page 1534, first column lines 7-13 teach "Preclinical studies have demonstrated the effectiveness of CpG oligonucleotides (ODNs) in the prevention and treatment of both upper and lower allergic airway disease [7-11]. Data from ongoing human trials using CpG ODNs suggest that it is a safe and well-tolerated agent that seems promising for the treatment of allergic airway inflammation." Also, page 1536, first column lines 33-43 teach "Mice that received immunotherapy with CpG ODNs alone, as well as CpG ODNs along with allergen, prior to receiving RAE, had significantly inhibited development of GC hyperplasia and AHR. In those studies, the authors also characterized the epithelial changes by morphometric analyses and found that CpG ODNs also inhibit the amount of stored mucin in airway cells. Increased amounts of stored mucin (and subsequent GC degranulation) contribute to the pathogenic mechanisms for patients with asthma, including airway narrowing, exacerbations and accelerated decline in lung function."

Finally, the office action asserts that one of skill in the art would not accept on its face that the working examples are correlative or representative of methods of treatment. On page 11 it is stated that "No correlation is taught in the instant disclosure between the ability of these CpG containing oligonucleotides to induce a Th1 response in vitro (e.g. amount of IL-6 induction) and their ability to treat asthma in vivo." The claimed invention is not a method for treating asthma. The claimed method relates to a method for shifting to a Th1 immune response.

As described above, the specification includes working examples demonstrating that CpG oligonucleotides are useful in producing a Th1 biased immune response. In particular Table 5 shows the production of Th1 cytokines in response to different CpG containing oligonucleotides. Applicants have asserted in the specification that the class of oligonucleotides having a CpG motif is useful for producing a biased Th1 immune response. Krieg et al, cited by the Examiner, supports Applicants' assertions and data. The examiner has not provided any evidence to support the assertion that one of skill in the art would not accept on its face that the working examples are correlative or representative of methods of treatment.

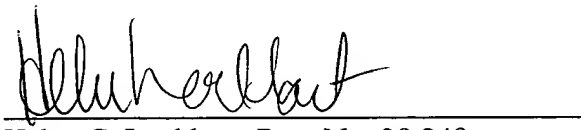
The instant patent application includes a significant amount of data, demonstrating that CpG oligonucleotides worked in vitro and in vivo as described and supporting their therapeutic use. Thus, the full scope of the claims was enabled at the time the patent application was filed.

Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

Respectfully submitted,



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Docket No. C1039.70022US00
Date: May 1, 2006
x05/01/06x

[743] TLR9 Agonist Immunomodulator Treatment of Cutaneous T-Cell Lymphoma (CTCL) with CPG7909. Session Type: Oral Session

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CPG 7909 belongs to a new class of chemically defined CpG immunomodulators that target dendritic cell TLR9 receptors inducing IL-12, IFN-gamma, and NK cell function. The rate and durability of response to CPG 7909 was investigated in refractory patients with recurrent or advanced CTCL, who had failed one or more systemic therapies. Dose escalation with weekly sc dosing of patients at 0.08, 0.16, 0.24, or 0.28 mg/kg (3 patients/cohort) for 24 weeks is nearing completion. Additional patients continue to receive treatment at 0.32 (4 patients) or 0.36 mg/kg (12 patients). Clinical response, monitored by Composite Assessment of Index Lesion Disease Severity (CA) and Physician's Global Assessment of Clinical Condition, has been documented. Of 28 patients enrolled, 7 (25%) have achieved objective clinical response, 5 with partial response (PR) and 2 with complete response (CR). Eleven patients have maintained stable disease (SD), while 10 have had progressive disease (PD). Eight patients have completed 24 weeks of treatment (5 SD, 2 PR, 1 CR) with 12-16 weeks of response while on study. Six patients (3 SD, 2 PR,1 CR) are currently ongoing in the study. Three patients (2 PR, 1 SD) continue to receive long term CPG 7909 at 0.12 mg/kg (58 total doses), 0.28 mg/kg (34 total doses) or 0.32 mg/kg (29 total doses) in a follow on protocol. Responses have been maintained up to 46 weeks.
Weekly doses up to 0.36 mg/kg have been well tolerated. Most reported adverse events have been of CTC grade 1 or 2. The most common are dose-related local injection site reactions (erythema, induration, edema, inflammation and pain) and mild or moderate flu-like symptoms (fatigue, rigors, fever, arthralgia). Four patients had CTC grade 3 drug related AEs: one decreased lymphocyte count (0.08 mg/kg), one increased gamma glutamyl transferase (0.16 mg/kg), one decreased absolute polys (0.36 mg/kg) and one fatigue (0.36 mg/kg).
Enrollment in the phase II portion of the study is ongoing and compares results of patients randomized to receive either 10 mg or 25 mg sc weekly for 24 weeks (equating to effective doses seen in dose escalation).

Clinical Response with CPG 7909 - 16 M, 12 F

Dose	N	Disease Stage	CR	PR	SD	PD
0.36 mg/kg	12	IB (7), IIB, III (3), IVA	0	2	6	4

0.32 mg/kg	4	IIA, IIB, IVA (2)	1	0	1	2
0.28 mg/kg	3	IB (2), III	0	1	2	0
0.24 mg/kg	3	IB, IIB (2)	0	1	1	1
0.16 mg/kg	3	IB (2), IIA	1	1	1	0
0.08 mg/kg	3	IB (2), IVA	0	0	0	3
Total	28		7%	18%	39%	36%

Abstract #743 appears in Blood, Volume 104, Issue 11, November 16, 2004
Keywords: Cancer immunotherapy|Phase II|Dendritic cell

Tuesday, December 7, 2004, 08:00 AM

Simultaneous Session: Lymphoma - Therapy with Biologic Agents (8:00 AM-10:00 AM)

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Session Type: Oral Session

Authors: Youn Kim, Michael Girardi, Madeline Duvic, Timothy Kuzel, Alain Rook, Brian Link, Lauren Pinter-Brown, Carol Comerci, Sonja McAuley, Tess Schmalbach

Date/Time: Tuesday, December 7, 2004 - 08:00 AM

Session Info: Simultaneous Session: Lymphoma - Therapy with Biologic Agents (8:00 AM-10:00 AM)